Errata FDA BRIEFING DOCUMENT
NDA 202293 Dapagliflozin
Endocrinologic and Metabolic Drugs Advisory Committee meeting
July 19, 2011

1. Page 9 states "The applicant conducted a 24-week trial in diabetics (MB102029) with moderate renal impairment with the main purpose of assessing the safety of dapagliflozin in this specific population."

   Correction:
   Efficacy was assessed at 24 weeks, but this trial assessed safety during a 24 week short term and a 52 week short plus long term period.

2. Table 1 on page 10 includes a 10 mg and 20 mg dose for study MB102013.

   Correction:
   These doses were not included in this study.

3. Page 16 under Comparison between dapagliflozin and metformin, it is stated that "For Study MB102021, the mean difference between dapagliflozin plus metformin treatment and metformin alone was 0.7% (95% CI -0.94, -0.45)."

   Correction:
   This difference was -0.7%.

4. On page 17 under Lack of efficacy in patients with moderate renal impairment, severe renal impairment is defined as estimated GFR ≥29 mL/min/1.73 m^2 and ≤ 15 mL/min/1.73 m^2.

   Correction:
   The definition for severe renal impairment should read: estimated GFR ≥15 mL/min/1.73 m^2 and ≤ 29 mL/min/1.73 m^2.

5. On page 27, Table 13 describes risk factors for breast cancer at baseline in treated patients.

   Correction:
   This table is for female patients only. The title should state "*Baseline Breast Cancer Risk Factor Summary Phase 2b and 3 Pool, Treated Female Subjects*"

6. On page 34, Table 18 is entitled *Recurrence of Genital Infection in the Short-term Placebo Controlled Pool.*

Correction:
This table is for the short term **plus long term** placebo controlled pool.

7. One page 34, the rate of genital infection in the short-term plus long-term period is described as "consistent with those in the short-term treatment period only. The total in the dapagliflozin treated group was 160 patients (14.5%) and the total in the placebo treated group was 18 patients (5.2%)."

   Correction:
   The rates stated are in female patients only. The numbers/rates in the short plus long-term period for both males and females are 213 (9.9%) in dapagliflozin treated patients and 20 (2.9%) in placebo patients.

8. On page 34, at the end of page describing Figure 3, it is stated that by eight months, those treated with dapagliflozin 5 and 10 mg were at more risk than the 2.5 mg treated patients.

   Correction:
   By eight **weeks**, those treated with dapagliflozin 5 and 10 mg were at more risk than the 2.5 mg treated patients.

9. On page 41, Table 25 reports the SE for 4-week BUN in placebo patients as 1.0.

   Correction:
   This should be 0.1.

10. On page 43 the document states "The magnitude of the mean decreases (eGFR and CrCl) were consistently larger in the 30 to 44 mL/min/1.73 m^2 subgroup compared with the 45 to 59 mL/min/1.73 m^2 subgroup."

    Correction:
    The magnitude of mean decreases were larger in the 45 to 59 mL/min/1.73 m^2 subgroup compared to the 30 to 44 mL/min/1.73 m^2 subgroup.

11. On page 74, the document states:
    "At the time of writing this review, 10 subjects were reported as having been diagnosed with bladder cancer in the phase 2b and phase 3 clinical trials on dapagliflozin. Nine of these cases occurred in the active treatment arms and one in a placebo arm. All of these diagnoses were made in male subjects between the ages of 49 and 76. Diagnoses were made between study day 43 and 727. Total follow-up of male patients randomized to dapagliflozin was 2,237.1 subject-years (Table 4). With nine cases of bladder cancer occurring during this time, this rate amounts to 402 (95% CI, 184 – 764) new cases per 100,000 subject-years. This compares to 1 case during 989.8 subject-years in controls, or 101 (95% CI, 1.3 – 562) new cases per 100,000 subject-years. The two-sided p-value comparing the incidence of bladder cancer between active treatment and controls was 0.28 (Fisher's exact). The rate ratio

between active treatment and control was 3.98 [95% CI, 0.51 – 31.4]. These estimates are pooled summary estimates and do not take heterogeneity between clinical trials into account, including potential imbalances in active treatment versus control ratios that may introduce confounding.
Based on SEER data, only two cases (2.05) would be expected in the male dapagliflozin population (Table 4) at a rate of 91.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 4.39 (95% CI, 2.01 – 8.33), p<0.001. Consistent with actual occurrence, one case would be expected among the male controls."

Correction:
"The original review included ten cases of bladder cancer in male participants of the dapagliflozin clinical trials program. The sponsor recently provided exposure rates from studies D1690C00018 and D1690C00019, which were not included in the original review and where three of the ten cases occurred. The complete set of Phase 2b and 3 clinical trial participants was used to update estimates of incidence rates, incidence rate ratios and standardized incidence ratios (SIR) for bladder cancer. SIR were calculated comparing observed cases of bladder cancer with dapagliflozin to expected cases based on the Surveillance, Epidemiology, and End Results (SEER) database. Estimates from SEER were age- and sex-matched and adjusted for an increased risk for bladder cancer among diabetic patients.
Total follow-up of male patients randomized to dapagliflozin was 3007.1 subject-years. With nine cases of bladder cancer occurring during this time, this rate amounts to 299.3 (95% CI, 136.6 – 568.1) new cases per 100,000 subject-years. This compares to one case during 1696.6 subject-years in controls, or 58.9 (95% CI, 0.8 – 327.9) new cases per 100,000 subject-years. The incidence rate ratio between active treatment and control was 5.08 (95% CI, 0.70 – 222.6), two-sided p=0.15 (Fisher's exact).
Based on SEER data, only three (3.03) cases of bladder cancer would be expected in the male dapagliflozin exposed population at a rate of 100.6 new cases per 100,000 subject years. The standardized incidence ratio of observed versus expected cases in males exposed to dapagliflozin was 2.98 (95% CI, 1.36 – 5.65), p=0.008. Almost 2 cases (1.87) would be expected among controls, where only case was observed.